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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STAPLES, MARK	
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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/769,578	LOWERY ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *16-18 and 25-27* is/are withdrawn from consideration.

5)☒ Claim(s) *28* is/are allowed.

6)☒ Claim(s) *1, 2, 5, 7-15, 19-21, 23, 24, and 29-33* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/15/2007 has been entered.

2. Applicants' amendment of claims 1, 9, and 19; the cancellation of claims 3, 4, 6, and 22; and submission of new claim 30-33 in the paper filed on 06/15/2007 is acknowledged. Claims 16-18 and 23-27 are withdrawn.

Claims 1, 2, 5, 7-15, 19-21, 23, 24, and 28-33 are pending and at issue.

Applicants' arguments filed on 06/15/2007 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Response to Arguments

3. Applicant's arguments filed on 06/15/2007 with respect to claims 1, 2, 7-10, 12-15, 19-21, 23, and 24 have been considered but are moot in view of the new ground(s) of rejection.

In view of the new grounds of rejection, the allowability of claim 29 is withdrawn.

Claim Objections

4. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 already recites that the donor-product is formed by the catalytically active enzyme.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the first and second fluor of the FRET pair are not identified and it is thus also unclear whether they

are intended and if so, where they are located, i.e., what molecule(s) each might be attached to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 1, 2, 7-9, 12-15, 30, and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by Patton (May 2002).

Regarding claims 1, 8, 10, 30, and 31, Patton teaches an homogenous assay method for directly detecting a donor-product produced in a group transfer reaction (see section 3.6 on p. 15, where the 3rd paragraph describes an homogenous assay), the method comprising:

a) reacting a donor molecule, ADP-ribose, comprising a nucleotide attached to a covalent adduct/moiety, X which is NAD or 1,6-etheno NAD, with an acceptor which is a protein substrate in the presence of a catalytically active enzyme which is ADP-ribosyltransferase, such that the donor molecule is partially consumed (see 1st and 3rd paragraphs of section 3.6 on p. 15);

b) forming the donor-product and an acceptor-X, mono-ribosylated protein;

c) contacting the donor-product with a first complex comprising an antibody that specifically recognizes the donor-product in the presence of a donor-molecule which is an anti-ADP ribose antibody (see 3rd paragraph of section 3.6 on p. 15) and a detectable tag that is specifically displaced from the antibody by the donor-product and is capable of producing an observable of fluorescence (see 3rd paragraph of section 3.6 on p. 15);

d) competitively displacing the detectable tag of the first complex by the donor- product to generate a second complex and a displaced detectable tag resulting in the production of an observable; and

e) detecting a change in the observable produced by the detectable tag in the first complex and the displaced detectable tag (see 3rd paragraph of section 3.6 on p. 15).

Regarding claim 2, Patton teaches that as little as 1 pmol of ADP ribosylated proteins can be detected, quantifying the observable (see next to last sentence of section 3.6 on p. 15).

Regarding claim 7, Patton teaches 1,6-etheno NAD which is a detectable tag where the fluorescent molecule is conjugated to the a nucleotide (see 3rd paragraph of section 3.6 on p. 15).

Regarding claim 9, Patton teaches protein kinases (see p. 11, 1st sentence of 1st full paragraph).

Regarding claims 12-14, Patton teaches that the analysis of post-translational modifications/functional changes, such as ribosylating proteins, can be used to clinically

screen samples for therapeutic effects such as cancer treatment discovery (see Conclusion section on p. 27).

Regarding claim 15, Patton teaches the use of micoarrays (see last sentence on p. 27).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 2, 7, 8, 10, 13, and 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (1985, cited on the IDS) and Giovane et al. (1985).

Regarding claims 1, 8, 10, 30, and 31, Meyer et al. teach an immunoassay method for directly detecting a donor-product produced in a group transfer reaction (see especially the last sentence of the Abstract), the method comprising:

a) reacting a donor molecule, ADP-ribose, comprising a nucleotide attached to a covalent adduct, X which is NAD, with an acceptor which is a protein substrate in the presence of a catalytically active enzyme which is ADP-ribosyltransferase, such that the donor molecule is partially consumed (entire article, especially Abstract and paragraph 4 and 8 under the Discussion section on p. 164);

b) forming the donor-product and an acceptor-X, mono-ribosylated protein;

c) contacting the donor-product with a first complex comprising an antibody that specifically recognizes the donor-product in the presence of a donor-molecule which is an anti-ADP ribose antibody (see 1st full paragraph on p. 164) and a detectable tag that is specifically displaced from the antibody by the donor-product and is capable of producing an observable of immunofluorescence (see paragraph 8 under the Discussion section on p. 164);

d) competitively displacing the detectable tag of the first complex by the donor- product to generate a second complex (see 4th sentence of Abstract: "The antibodies obtained with this antigen were specific for free or protein-bound ADP-ribose groups" and as is well known in the art both these ADP ribose groups can then competitively displace one another from the antibody) and a displaced detectable tag resulting in the production of an observable (see paragraph 8 under the Discussion section on p. 164); and

e) detecting a change in the observable produced by the detectable tag in the first complex and the displaced detectable tag.

Regarding claim 1, Meyer et al. do not specifically teach a homogenous assay method.

Regarding claim 13, Meyer et al. teach wherein the molecule is capable of altering the function of the acceptor (see paragraph 8 under the Discussion section on p. 164).

Regarding claim 1 and 7, Giovane et al. teach a homogenous fluorescence assay using εNAD (also referred to as 1,6-etheno NAD, see entire article, especially abstract and Figure 1).

Regarding claim 2, Giovane et al. teach fluorescent measurements, that is, quantifying an observable (see section 2.5 on p. 192)

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Meyer et al. by performing an homogenous assay as suggested by Giovane et al. with a reasonable expectation of success. The motivation to do so is provided by Giovane et al. who teach that fluorescence change in the acceptor εNAD can be monitored by its binding to a complex which is added directly into the assay mixture without any separation steps. Further motivation is provided by Giovane et al. who also teach: "Our results leave no doubt that εNAD is interchangeable with NAD as a substrate . . . ." (see bottom of p. 193

to top of p. 194). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

9. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. and Giovane et al. as applied to claim 1 above, and further in view of Kawamitsu et al. (1984, previously cited).

Meyer et al. and Giovane et al. teach as noted above.

Meyer et al. and Giovane et al. do not teach a monoclonal antibody.

Kawamitsu et al. teach monoclonal antibodies which bind to poly adenosine diphosphate (poly(ADP-Rib) and to the monomer unit, Ado(p)-Rib-P, a nucleotide and donor-product from the diphosphate. A monoclonal antibody is a species of antibody. Kawamitsu et al. also teach how design of the immunogen and selection of clones can lead to a monoclonal antibody of desired specificity. This method is a fluorescence polarization immunoassay (FPIA).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the antibody of Meyer et al. and Giovane et al. by replacing it with a monoclonal antibody as taught by Kawamitsu which binds to the donor product with a reasonable expectation of success. The motivation to do use this approach is provided by Kawamitsu et al. who teach that that antibodies to Ado(p)-Rib-P can be successfully produced for detection of Ado(p)-Rib-P. Kawamitsu et al. further teach strategies for arriving at a desired antibody specificity. Thus, the

claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

10. Claims 9, 11, and 12, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. and Giovane et al. as applied to claim 1 above, and further in view of Seethala (2000, previously cited).

Meyer et al. and Giovane et al. teach as noted above.

Meyer et al. and Giovane et al. do not teach the limitations of claims 9, 11, and 12, 14, and 15.

Regarding claim 9, Seethala teaches a method comprising catalytic activity of tyrosine kinases (entire reference, especially title and abstract).

Regarding claims 11, Seethala teaches a method of measuring and comparing fluorescence polarization (entire reference, especially Figures 1 and 2).

Regarding claims 12, Seethala teaches a method for screening a chemical library of compounds for tyrosine kinase inhibitor (entire reference, especially p. 69, 1st paragraph under *Concluding Remarks*).

Regarding claim 14, Seethala teaches wherein the molecule is a drug, capable of a therapeutic effect (entire reference, especially p. 61, 4th sentence of 2nd column).

Regarding claim 15, Seethala teaches a high throughput technique comprising a mutliwell plate, microplate wells (entire reference, especially p. 66, 2nd column, 3rd sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Meyer et al. and Giovane et al. by using a kinase in the screen for compounds having a therapeutic effect in high throughput technique as suggested by Seethala with a reasonable expectation of success. The motivation to do so is provided by Seethala who teach that that a competitive assay increases assay sensitivity and throughput (see 1st sentence of Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

11. Claims 19-21, 23, 24, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al., Giovane et al., Seethala, and Bredehorst (1978, previously cited).

Regarding claims 19, 29, and 30, Meyer et al., Giovane et al., and Seethala teach as noted above.

Regarding claims 19, Seethala teaches a method of measuring and comparing fluorescence polarization (entire reference, especially Figures 1 and 2).

Regarding claim 19, Giovane et al. teach that a fluorophore can be a conjugated as a dinucleotide (see Abstract).

Regarding claim 30, Giovane et al. teach that a donor-conjugated to a fluorophore, εNAD, undergoes an energy change, which is a blue shift of the emission spectra, upon binding to the macromolecule EF-2 (see Results section on p. 192). As claim 30 is indefinite (see rejection above), it has been interpreted here according to the

recited limitations; those being, that there is one fluorophore conjugated to the donor-product, which undergoes an energy transfer/change.

Regarding claims 20, and 21, Seethala teaches a method comprising catalytic activity of tyrosine kinases (entire reference, especially title and abstract).

Regarding claim 23, Seethala teaches where the fluorophore is fluorescein (see Figure 2).

Regarding claim 24, Seethala teaches a method for screening a chemical library of compounds for tyrosine kinase inhibitor (entire reference, especially p. 69, 1st paragraph under *Concluding Remarks*).

Regarding claims 19, 29, and 30 Meyer et al., Giovane et al., and Seethala do not specifically teach an antibody to the donor product ADP.

Regarding claims 19, 29, and 30, Bredehorst et al. teach production of antibodies against ADP-ribose and analogs. Bredehorst et al. teach how design of the immunogen can lead to desired specificity. Bredehorst et al. further teach an antibody which recognizes ADP, a nucleotide and a donor-product. Bredehorst et al. also show that this same antibody can be specific to ADP which can be a donor-product (entire reference, especially Table 3). It is noted that none of claims 19, 29, or 30 have a limitation where the donor molecule is ATP and therefore do not have the additional limitation that the antibody to ADP must function to specifically bind ADP when ATP is

present. Thus the antibody to ADP as taught by Bredehorst et al. reads on claims 19, 29, and 30.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the macromolecule of Meyer et al., Giovane et al., and Seethala by replacing it with an antibody as taught by Bredehorst et al. which binds to the donor product, ADP, in order to detect ADP with a reasonable expectation of success. The motivation to do so is provided by Bredehorst who teach that that antibodies to ADP can be produced for detection and quantification of ADP. Bredehorst et al. further teach strategies for arriving at a desired antibody specificity. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

12. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. and Giovane et al. as applied to claim 31 above, and further in view of Otterness et al. (1990).

Meyer et al. and Giovane et al. teach as noted above.

Meyer et al. and Giovane et al. do not teach a sulfotransferase.

Otterness et al. teach a sulfotransferase (see Title).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme of Meyer et al. and Giovane et al. by replacing it with a sulfotransferase as taught by Otterness et al. with a

reasonable expectation of success. The motivation to do use this approach is provided by Otterness et al. who teach that sulfation by sulfotransferase is an important pathway especially in the formation of drugs (entire article, especially 1st paragraph on p. 34). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

13. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. and Giovane et al. as applied to claim 31 above, and further in view of Kouri et al. (1990).

Meyer et al. and Giovane et al. teach as noted above.

Meyer et al. and Giovane et al. do not teach UDP-glucuronosyltransferase.

Kouir et al. teach UDP-glucuronosyltransferase and its use with a conjugate fluorophore, 4-methylumbelliferone (see Enzyme Assays on p. 38).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the enzyme of Meyer et al. and Giovane et al. by replacing it with UDP-glucuronosyltransferase as taught by Kouri et al. with a reasonable expectation of success. The motivation to do use this approach is provided by Kouri et al. who teach that monitoring UDP-glucuronosyltransferase is important in ascertaining the toxicity of compounds (entire article, especially Chart 3). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

14. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. and Giovane et al. as applied to claim 1 above, and further in view of Kawamitsu et al. (1984).

Meyer et al. and Giovane et al. teach as noted above.

Meyer et al. and Giovane et al. do not teach a monoclonal antibody.

Kawamitsu et al. teach monoclonal antibodies which bind to poly adenosine diphosphate (poly(ADP-Rib) and to the monomer unit, Ado(p)-Rib-P, a nucleotide and donor-product from the diphosphate. A monoclonal antibody is a species of antibody. Kawamitsu et al. also teach how design of the immunogen and selection of clones can lead to a monoclonal antibody of desired specificity.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the antibody of Meyer et al. and Giovane et al. by replacing it with a monoclonal antibody as taught by Kawamitsu which binds to the donor product with a reasonable expectation of success. The motivation to do use this approach is provided by Kawamitsu et al. who teach that that antibodies to Ado(p)-Rib-P can be successfully produced for detection of Ado(p)-Rib-P. Kawamitsu et al. further teach strategies for arriving at a desired antibody specificity. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Allowable Subject Matter

15. Claim 28 is allowable.

16. The following is a statement of reasons for the indication of allowable subject matter: No prior art was found which teaches or fairly suggests the limitations of claim 28. As conveyed in the Declaration of Robert Lowry under 37 CFR 1.132 filed on 01/02/2007, the prior art does not teach or fairly suggest the detection of the donor product ADP by an antibody specific to ADP, in the presence of the donor ATP. No prior art was found by Examiner which teaches or fairly suggests the use of an antibody specific to ADP for detection of ADP in the presence of ATP.

Conclusion

17. Claim 28 is allowable.

18. Claims 1, 2, 5, 7-15, 19-24, and 29-33 are not free of the prior art.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
Examiner
Art Unit 1637
August 2, 2007

MS

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

8/6/07